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Sowing the Seeds of a Fruitful Harvest: Hematopoietic Stem Cell Mobilization

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Abstract

Hematopoietic stem cell transplantation is the only curative option for a number of malignant and non-malignant diseases. As the use of hematopoietic transplant has expanded, so too has the source of stem and progenitor cells. The predominate source of stem and progenitors today, particularly in settings of autologous transplantation, is mobilized peripheral blood. This review will highlight the historical advances which lead to the widespread use of peripheral blood stem cells for transplantation, with a look towards future enhancements to mobilization strategies.

Keywords

Hematopoietic stem cell (HSC); mobilization; granulocyte-colony stimulating factor (G-CSF); CXCR4; stem cell niche; AMD3100 (plerixafor)

Introduction

The first successful clinical cases utilizing peripheral blood stem cells (PBSC) for curative hematopoietic transplantation were reported over 26 years ago(1–5). Since then, PBSC have become the predominate source of hematopoietic stem cells (HSC) for transplantation. This review will highlight the history of stem cell research which planted the initial seeds for PBSC harvesting; the current state of clinical mobilization and what we have learned over the last two and half decades of practice; and the outlook for clinical enhancement in the future.

Sowing the Seeds: Early Mobilization Research

Early work establishing the foundation of hematopoietic mobilization began over 60 years ago (Figure 1). Restoration of hematopoiesis in irradiated animals by spleen and/or bone marrow (BM) derived cells was reported in the early 1950s (6–8). Shortly thereafter, it was demonstrated that allogeneic skin grafts were tolerated in mice who had received lethal

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irradiation followed by a hematopoietic transplant (9). This lead to the concept of chimerism, i.e., donor cells reconstituting the irradiated host, which was confirmed in later studies (10–14). In the 1960's, Till and McCulloch and colleagues published hallmark studies showing that single clonogenic cells existed within the bone marrow that could self-renew and restore hematopoiesis (15–20), thus the hypothesis of the *in vivo* existence of a hematopoietic stem cells was germinated. These early assays utilized lethally irradiated mice that were injected with bone marrow cells and showed macroscopic nodules that formed on/in the spleens proportional to the number of marrow cells injected (17). They hypothesized that the spleen colonies (colony-forming units-spleen (CFU-S)) were derived from a single cell, which they later demonstrated by analysis of chromosomal markers (20). These studies laid the groundwork for clinical hematopoietic transplantation.

In the 1930's, well prior to studies using isolated donor cells to recover hematopoiesis following irradiation, Woenckhaus performed experiments in which one rat, as part of a parabiotic pair, was lethally irradiated while the other rat was shielded with lead. One third of the pairs survived the procedure, suggesting a circulating radiation protection factor produced by the non-irradiated rat (21). A similar parabiotic experiment was also reported two decades later (22). As methods to assess DNA replication, and thus cell division, began to emerge, reports documented the presence of circulating, non-leukemic, blood cells capable of division outside of the bone marrow (23, 24). These experiments suggested that a large organ like the bone marrow was capable of exchanging cells through the peripheral blood system, providing a potential common pool of cells with proliferative capacity able to directly contribute to recovery after damage and maintain total system homeostasis.

In 1960, a report demonstrated the successful transplantation of cells with erythropoietic potential from normal circulating leukocytes (25). This was later expanded upon by Goodman and Hodgson to demonstrate the presence of a peripheral blood cell capable of hematopoietic reconstitution in lethally irradiated hosts (26). Later experiments utilizing CFU-S as a surrogate of HSC function suggested that peripheral blood leukocytes contained $1/100^{th}$ of the repopulating ability of bone marrow leukocytes (27). The presence of peripheral blood hematopoietic repopulating cells was later confirmed in transplantation studies in dogs (28–30).

These early studies in rodents and dogs suggested that peripheral blood could be an alternative source to bone marrow of cells with hematopoietic reconstituting potential. However, Lewis and colleagues in 1968 suggested that the frequency of repopulating cells (estimated to be $1/100^{th}$ that of marrow), was too low in peripheral blood and they concluded that "*with present techniques, the use of blood leukocytes for effecting hematopoietic grafts in man may not be technically feasible. In terms of present day knowledge, it is difficult to envision that circulating stem cells will be found to be of any great value to man.*" (27). Fortuitously, around the same time, researchers at the National Cancer Institute along with the International Business Machines Corporation jointly developed a continuous flow centrifuge (NCI-IBM Blood Cell Separator) as a means to isolate leukocytes for biopsy, or for subsequent infusion into granulocytic patients (31–33). This apheresis technique reduced one of the technical hurdles of acquiring enough peripheral blood repopulating units for transplantation.

In the early 1970's, several reports confirmed the presence of clonogenic hematopoietic progenitors in the peripheral blood of man (34–36), one of which utilized apheresis (36), thus planting the initial seeds for the potential to harvest HSCs from blood for transplant. However, early attempts at repetitive white blood cell transfusions from healthy twin donors did not result in durable engraftment (37, 38), presumably still due to the relatively low HSC cell number in peripheral blood compared to bone marrow. To compensate for low HSC

number, cryopreservation techniques were developed to allow for large pools of peripheral blood leukocytes to be collected (39), and transplants using cryopreserved peripheral blood cells were used to treat patients with chronic myeloid leukemia (CML), with some documented short term success (40–42). Several years later, many institutes began to report successful hematopoietic engraftment using cryopreserved cells acquired from multiple rounds of apheresis prior to transplantation (1–5).

While these early studies demonstrated some successes, multiple rounds of apheresis, over the course of many days and weeks, coupled with multiple cryopreservations and subsequent infusions of large volumes of cells made these early regimens impractical for wide clinical application. To expand the use of PBSC to a broader range of hematopoietic transplantation, more stem cells needed to be acquired in a shorter period of time. Several earlier reports assessing the bone marrow compartment following chemotherapy demonstrated an increase in hematopoietic progenitor activity (43–45). A report by Richman and colleagues further explored this phenomenon by assessing hematopoietic progenitors in the peripheral blood following administration of cyclophosphamide and adriamycin (46). These studies demonstrated that chemotherapy treatment could increase in hematopoietic progenitors in the blood by upwards of a 20 fold. Intriguingly, the authors proposed that chemotherapy could possibly be used as a means to facilitate acquisition of PBSC for transplantation. As a preliminary test of hypothesis they studied one patient in which they harvested bone marrow and apheresis products before and after chemotherapy. This single patient demonstrated that at baseline, they would need to perform 296 hours of apheresis to acquire the same number of hematopoietic progenitors as was obtained from the bone marrow harvest, but after chemotherapy, the amount of apheresis time would be reduced to only 11 hours (46). A similar conclusion was made several years later by Stiff and colleagues(47). These results suggested that another major hurdle for the clinical translation of PBSC as a viable alternative to bone marrow could be crossed; mobilization of HSC to the periphery with the use of chemotherapy to decrease the amount of apheresis procedures and transfusion volumes. This suggestion was confirmed in a number of subsequent studies (48, 49).

Enhancing the Harvest: Granulocyte-Colony Stimulating Factor

Today, the hematopoietic growth factor, granulocyte-colony stimulating factor (G-CSF) is widely used clinically to mobilize HSC for transplantation. Granulocyte colony-stimulating factor (G-CSF) was purified, cloned and produced recombinantly in bacteria between 1984 and 1986 (50–53). Although initially believed to be a pluripoietin as well an inducer of granulocyte differentiation, use of recombinant protein showed that G-CSF bound to a type 1 cytokine receptor (G-CSFR) to stimulate proliferation (54, 55) and differentiation (53) of several types of myeloid progenitor cells alone and in combination with other growth factors (56–58). The first clinical trials were performed in cancer patients receiving chemotherapy (59–62) leading to FDA approval in 1991. While G-CSF was being widely used successfully to treat neutropenia following chemotherapy, it was found that it increased the number of peripheral blood progenitor cells (63, 64). While early empiric regimens were variable, today, mobilization of HSC and HPC is accomplished with G-CSF administered at 5–10 ug/kg/day for 5–7 days in patients and normal donors, with one or more days of apheresis to achieve a minimum target dose $\geq 2\times10^6$ $CD34^+$ cells/kg patient body weight. PBSC transplant with G-CSF mobilized HSC and HPC has been quite successful and has changed the normal transplant paradigm, making PBSC the predominate source of HSC for transplant. G-CSF mobilized PBSC have been associated with more rapid engraftment, shorter hospital stay (65–68), and in some circumstances, superior overall survival compared to bone marrow (69).

While successful, G-CSF regimens are often associated with morbidity in the form of bone pain, nausea, headache, and fatigue (70–73), which can be lifestyle disruptive in normal volunteers. In a small population of normal donors, G-CSF has also been associated with serious toxicity, including enlargement of the spleen (74, 75) and splenic rupture (76–79), and the pro-coagulant effects of G-CSF can increase the risk of myocardial infarction and cerebral ischemia in high-risk individuals (80, 81). Despite success, G-CSF induced mobilization regimens also have high failure rates, failing to mobilize sufficient HSC, particularly for autologous mobilization, necessitating additional mobilization attempts or precluding transplantation (82–86). Unsuccessful initial HSC mobilization often leads to expensive additional mobilization attempts and may preclude autologous transplant altogether (87–89). In one study assessing 1040 patients undergoing mobilization for autologous transplant, it was found that 47% failed to collect even the minimum of 2×10^6 $CD34^+$ cells/kg in the first apheresis, and 22.5% did not reach this level even after 2 apheresis sessions (82). A recent study out of the Mayo Clinic demonstrated that 30% of multiple myeloma (MM) and 71% of non-hodgkin's lymphoma (NHL) patients failed to reach the "optimum" level of $CD34^+$ cell collection ($>5\times10^6$ cells/kg) (90). A recent economic analysis at M.D. Anderson Cancer Center determined that reducing the apheresis by 1 day has the potential to decrease the medicals costs by $6,600 (91). Thus, improved/alternative regimens and mobilizers are needed.

The New Branches of HSC Mobilization

While the discovery of enhanced peripheral progenitors following chemotherapy, and then after growth factors such as G-CSF and GM-CSF, altered the paradigm of clinical transplantation, lack of initial understanding of the mechanism of action of these cytokines hampered further development in the field, which relied primarily upon empiric trial. Clues to the mechanism of action of G-CSF were not inherently obvious; however, early on it was appreciated that the mobilization mechanisms may be both HSPC intrinsic and extrinsic. A seminal paper published in 2002 (92) linked G-CSF mobilization to disruption of the SDF1/CXCR4 axis and led to a number of studies showing that altering this pathway by a variety of methods led to PBSC mobilization in varying degree. Numerous mobilization agents have sprouted from these early discoveries (Figure 2).

One of the most successful mobilizing agents to come along after G-CSF is the CXCR4 antagonist AMD3100 (Plerixafor; Mozobil™), which is capable of mobilizing HSC and HPC alone and in combination with G-CSF (93–98) and received FDA approval in 2008. Other CXCR4 antagonists such as T140 (99) and T134 (100) have also been reported to mobilize HSPC as well as CXCR4 partial agonists, including (met)-SDF-1β (101), CTCE-0214 (102), and CTCE-0021 (98). These agents are believed to initiate mobilization by antagonizing the CXCR4 receptor thus breaking the retentive bond between HSC and HPC and their SDF-1 producing stromal microenvironmental support. Betafectin (103, 104), sulfated polysaccharides (Fucoidan) (105–107), sulfated colominic acid (108), and the smaller glycosaminoglycan (GAG) mimetics (109), which appear to alter plasma SDF-1α levels (107–109), enhance matrix metalloproteinase-9 (MMP-9) production (103, 106, 109) and increase CXCR4 receptor function (108) among other mechanisms are also capable of enhancing HSPC mobilization.

While these mobilization strategies focused on disruption of the SDF-1α/CXCR4 interaction within the bone marrow microenvironment and/or alteration of the chemotactic gradient between blood and marrow, other mechanistic studies based upon knowledge of integrin adhesion interactions between hematopoietic cells and their stromal niches led to strategies designed to "untether" HSPC from the niche. Hematopoietic mobilization has been achieved by disrupting the VLA-4/VCAM-1 axis, with antibodies against VLA-4 (110, 111),

antibodies against VCAM-1 (112, 113), or a small molecule inhibitor of VLA-4 (BIO5192) (114). Similarly, disruption of the Eph-ephrin A3 axis with a soluble EphA3-Fc fusion protein (115) or treatment with defibrotide(116), an adenosine receptor agonist which disrupts P-selectin (117) and intercellular adhesion molecule-1 (ICAM-1) (118), also enhance mobilization.

Interest in chemokines in the 1990's spurred by the identification of multiple classes of chemotactic peptides that affect HSPCs led to the identification of an alternate chemokine pathway involved in mobilization (119, 120). The CXCR2 agonists IL8, GROβ and GRO$\beta_{\Delta 4}$ cause rapid HSPC mobilization within 15 minutes of treatment (121–123). In contrast to CXCR4, CXCR2 is not expressed on HSPC, and mechanistic studies identified that mobilization was mediated through induction of matrix metalloproteinase-9 disrupting hematopoietic retention in the niche (123, 124), and demonstrating that mobilization agents can target non-hematopoietic cells to illicit mobilization responses.

Recent evidence also suggests that disruption of fatty acid signaling can alter hematopoietic trafficking and be used as a pharmaceutical tool to enhance HSPC mobilization. Sphingosine-1-phosphate (S1P) can act on HSC and HPC through the S1P receptor S1P1 (125), and alter CXCR4/SDF-1α signaling and chemotaxis (125–127). S1P has been previously reported to direct trafficking of immature B cells (128) and trafficking of HSPC from blood, bone marrow and lymph tissues (129). G-CSF treatment results in an increase in peripheral S1P concentration directing HSPC chemoattraction to the periphery, resulting in mobilization (130). Additional reports have supported the hypothesis that a S1P signaling gradient can regulate HSPC trafficking and mobilization (131–134). Endocannabinoids, members of the arachidonic acid family of fatty acids, are also capable of altering HSPC trafficking and enhancing G-CSF mobilization through effects on cannabinoid receptors expressed on HSPC (135). Prostaglandin E_2 (PGE_2), another member of the arachidonic acid family, acts in a Yin and Yang relationship with G-CSF (135) and regulates CXCR4 expression on HSC and HPC and facilitates homing and engraftment during transplantation (136). Blocking PGE_2 signaling in the bone marrow with FDA approved NSAIDs alters HSC and HPC retention in the stromal niche, resulting in enhanced HSPC trafficking and mobilization in combination with multiple mobilizing agents (137).

Intriguingly, G-CSF mobilization is reduced in chemically sympathectomized mice; mice treated with the β-blocker propanolol; or mice genetically deficient in the gene for dopamine β-hydroxylase (Dbh), an enzyme that converts dopamine into norepinephrine, demonstrating that mobilization requires peripheral β_2-adrenergic signals (138). This study also demonstrated that G-CSF attenuated osteoblast function, via the sympathetic nervous system (SNS), resulting in osteoblasts having a marked flattened appearance. In addition to the bone marrow microenvironmental niche, human $CD34^+$ cells also express β_2-adrenergic and dopamine receptors that are upregulated after G-CSF treatment (139), and neurotransmitters have been demonstrated to serve as direct chemoattractants to hematopoietic cells (139) and increase CXCR4 expression (140). Epinephrine treatment also results in mobilization (139). These studies suggest that targeting of the SNS may serve as an adjunct therapy to enhance mobilization, though these strategies as of now are not specific in targets and would likely lead to many complications in patients and healthy donors.

Planting New Ground

At present, the wide array of agents that have been shown to mobilize HSC and HPC, leads us to conclude that we do not truly fully understand the biology of enhanced HSPC trafficking, and only a better understanding of this process can lead to better mobilizers and/or regimens. However, these new seeds of knowledge on mechanisms of action should not

remain ungerminated in the quest for the "perfect" or "optimal" mobilizing agent. Taking cues from the fields of chemotherapy and microbiology, combinations of agents often provide additive/synergistic and unique actions. The small molecule CXCR4 antagonist Plerixafor (AMD3100), which was shown in preclinical combination studies with G-CSF to enhance mobilization compared to G-CSF alone (93, 141–144), is now approved by the FDA for mobilization of PBSC in patients with NHL and MM, however a significant portion of patients still fail to mobilize sufficient numbers even after plerixafor administration. The use of Plerixafor can also come at a cost of >$25,000 per patient in some settings compared to G-CSF (145), suggesting that preemptive use in all patients in not a sound pharmacoeconomic strategy. To save cost associated with the use of plerixafor, a number of centers have advocated a risk-adapted approach whereby plerixafor is added after 4 days of filgrastim only in those patients who show evidence of "suboptimal" mobilization based on assessment of peripheral blood $CD34^+$ cell measurement (146–148) or alternatively on the basis of the $CD34^+$ cell dose collected on the first day's apheresis (148). However, as the target or "acceptable" $CD34^+$ cell dose, as well as the "acceptable" number of aphereses in which this achieved, vary somewhat by institution, precise recommendations also vary; currently no standard algorithm exists. At Indiana University, we target for a minimum $CD34^+$ cell dose of 10×10^6/kg for MM (for potentially tandem or second late transplantation), and 5×10^6/kg for NHL patients. To minimize utilization of apheresis resources, we also attempt to collect the target dose in only 1–2 aphereses if possible. Therefore, patients begin mobilization with G-CSF (10 μg/kg/day) for 4 days. If the first day's collection on day 5 is less than half of the target, plerixafor is added on the evening of day 5 (G-CSF continued), and apheresis performed the next day. Thus, while Plerixafor plus G-CSF has clearly made an impact on the ability to mobilize patient populations known to be difficult to mobilize, the need to search for more effective, and less costly, mobilizing agents still remains.

As described earlier, NSAIDs alter HSC and HPC retention in the stromal niche, resulting in enhanced HSPC trafficking and when used with G-CSF results in a PBSC graft that restores neutrophils and platelets faster than observed with the PBSC grafts mobilized by G-CSF alone (137). This finding represents an exciting opportunity to utilize a highly effective but inexpensive FDA approved drug to enhance PBSC mobilization and may be more appropriate for preemptive strategies, eliminating the need for guesswork on "poor" versus "good mobilizers" to decide who receives treatment and who does not.

Another fertile area to cultivate may in fact be the use of rapid mobilizers alone. In the studies reported to date, it is clear that these agents, particularly chemokines and their receptors, differ dramatically in their mobilization mechanism compared to G-CSF. These agents mobilize in minutes to hours compared to days for G-CSF. They are, however, usually less active than G-CSF based upon numbers of hematopoietic progenitors mobilized. However, in preclinical studies, the PBSC graft mobilized by these agents appears to contain a population of more immature HSPC with inherent superior engraftment capacity compared to G-CSF alone (149–151). A combination that we have recently investigated utilizes the CXCR4 antagonist AMD3100 with the CXCR2 agonist $GRO\beta_{\Delta4}$. When these 2 agents are administered either simultaneously or within 5 minutes of each other, a level of HSPC mobilization is reached within 15 minutes that is equal to that of G-CSF used alone for 4 days (150). Similarly, in primary competitive transplantation models, the graft mobilized by combination of AMD3100 plus GROβ showed equal or slightly better chimerism compared to a PBSC graft mobilized by a four day regimen of G-CSF. However, in secondary non-competitive transplant models transplant of equal numbers of bone marrow cells harvested at 6 months from mice who had received AMD3100 plus GROβ mobilized grafts showed significantly enhanced chimerism compared to mice receiving G-CSF mobilized PBSC, clearly suggesting superior engraftment and enhanced competitiveness of the primary graft

compared to G-CSF. Translation of the rapid mobilizer strategy to clinical transplantation may in fact alter the transplant paradigm and allow for transplant without graft cryopreservation, and the inherent loss of stem and progenitor cells by freezing, thaw and wash. The level of mobilization seen in mice with this combination suggests that the need for multiple days of apheresis can be significantly reduce or even eliminated. Since recombinant GROβ has been administered in man, it will be interesting to see if preclinical findings can be translated.

Defining a successful harvest

The inherent enhanced reconstituting capacity of PBSC grafts mobilized in part through agonism of the CXCR4 and CXCR2 receptors, or use of NSAIDs with G-CSF raise the issue of defining an “optimal graft” as defined by CD34+ cells per kg body weight. Clearly, CD34+ cell number is a useful current guideline for transplant that is based on the paradigm of using G-CSF as a single agent mobilizer. Preclinical data with AMD3100 and GROβ have suggested that there is a qualitative difference in the PBSC mobilized by these agents (93, 121, 150, 152, 153). Similarly, in a trial exploring AMD3100 as a single agent without G-CSF, reduced CD34+ cell number with AMD3100 was seen compared to G-CSF, yet the transplanted patients showed rapid and durable trilineage hematopoiesis (154). It will remain to be determined if minimum CD34 count, i.e., 2×10^6/kg will be useful as a guideline for grafts mobilized by other agents.

Conclusion

G-CSF mobilized PBSC have had a significant impact on the expansion of hematopoietic transplantation as a curative option for numerous malignant and non malignant diseases. The flurry of mechanism based research studies that has followed the largely clinical trial based development of G-CSF based PBSC mobilization identified new agents and potential pathways for improvements to mobilization, and has led to FDA approval for Plerixafor in combination with G-CSF for hard to mobilize patients. Preclinical studies have increased our understanding of HSPC trafficking and although clearly incomplete, we have reached a time where these new seeds of knowledge can and should be germinated to develop improved varieties of PBSC mobilization that based upon preclinical data may yield stronger and more robust effects.

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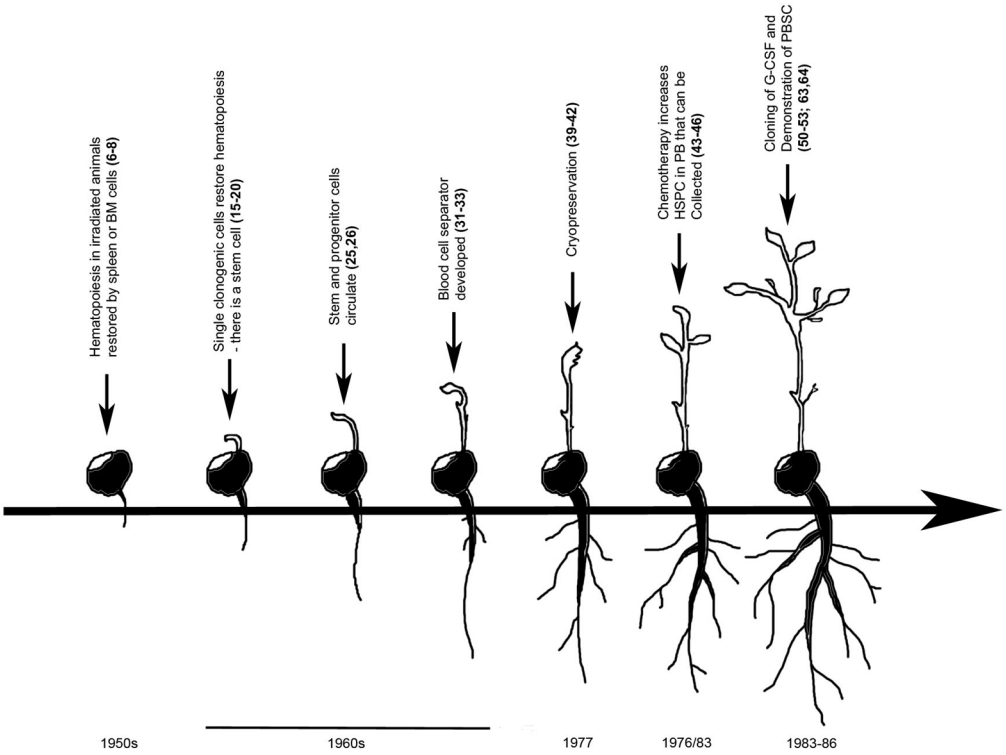

Figure 1.
Timeline of major advances leading to the use of peripheral blood stem cells for hematopoietic transplantation.

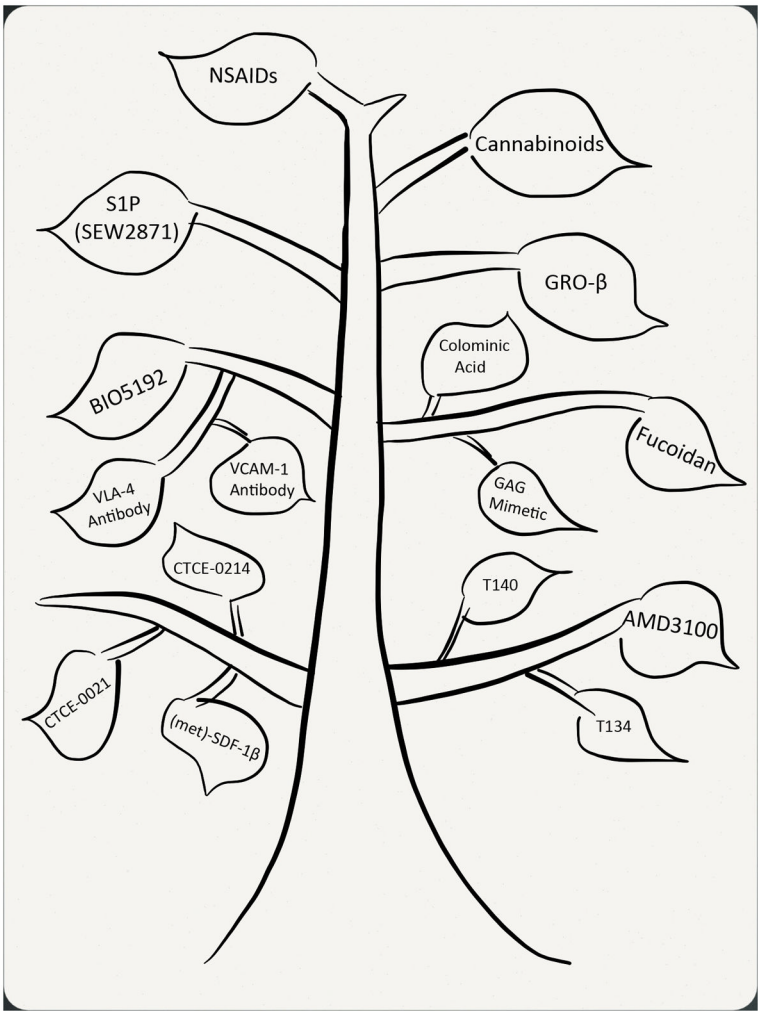

Figure 2.
The new branches of hematopoietic stem cell mobilization, showing alternative agents to G-CSF.